

ACVIM Consensus Statement

J Vet Intern Med 2005;19:123–134

Consensus Statements of the American College of Veterinary Internal Medicine (ACVIM) provide veterinarians with guidelines regarding the pathophysiology, diagnosis, or treatment of animal diseases. The foundation of the Consensus Statement is evidence-based medicine, but if such evidence is conflicting or lacking the panel provides interpretive recommendations based on their collective expertise. The Consensus Statement is intended to be a guide for veterinarians, but it is not a statement of standard of care or a substitute for clinical judgment. Topics of statements and panel members to draft the statements are selected by the Board of Regents with input from the general membership. A draft is prepared and input from Diplomates is solicited at the Forum and via the ACVIM Web site and incorporated in a final version. This Consensus Statement was approved by the Board of Regents of the ACVIM before publication.

Streptococcus equi Infections in Horses: Guidelines for Treatment, Control, and Prevention of Strangles

Corinne R. Sweeney, John F. Timoney, J. Richard Newton, and Melissa T. Hines

Disease caused by *Streptococcus equi* infection in horses, commonly referred to as strangles, was described in early veterinary science literature and first reported by Jordanus Ruffus in 1251. Although its official name is *S equi* subsp *equi*, there is compelling evidence that it is derived from an ancestral *S zooepidemicus* as a genovar or biovar of the latter. We have decided throughout the consensus statement to use the descriptive term *S equi* based on its widespread usage in the scientific literature over the past century. The following consensus statement reflects our current knowledge and opinion about clinical signs, pathogenesis, epidemiology, treatment, complications, and control of strangles. The information should aid veterinarians in devising control procedures and in the management of strangles outbreaks.

Clinical Signs

Strangles is characterized by abrupt onset of fever followed by upper respiratory tract catarrh, as evidenced by mucopurulent nasal discharge and acute swelling with subsequent abscess formation in submandibular and retropharyngeal lymph nodes. The name *strangles* was coined because affected horses sometimes were suffocated by enlarged lymph nodes that obstructed the airway. Severity of disease varies greatly depending on the immune status of the animal. Older horses often exhibit a mild form of the

disease characterized by nasal discharge, small abscesses, and rapid resolution of disease, whereas younger horses are more likely to develop severe lymph node abscessation that subsequently opens and drains.

Fever is the first clinical sign and persists as lymphadenopathy develops and abscesses mature. Pharyngitis causes dysphagia, and affected animals may become anorexic or reluctant to eat and often stand with the neck extended. Attempts to swallow food and water may be followed by reflux of these substances from the nares. Depression and listlessness are common signs. Pharyngitis, laryngitis, and rhinitis may occur and contribute to bilateral nasal discharge, which is serous initially and rapidly becomes mucopurulent and then purulent, profuse, and tenacious. Accumulation of purulent exudates may cause a snuffling or rattling upper respiratory noise. Nasal and ocular mucosa may become hyperemic, and there may be purulent ocular discharge from which *S equi* might be isolated.

Lymphadenopathy is a major clinical sign. The submandibular and retropharyngeal lymph nodes are about equally involved in *S equi* infections and become swollen and painful about 1 week after infection. The first sign of lymphadenopathy is often hot, diffuse, painful edema. Serum may then ooze from the overlying skin for several days, as the lymph node abscesses mature before rupturing to drain tenacious creamy pus, which does not have a foul odor. Other lymph nodes of the rostral neck (parotid, cranial cervical, and retropharyngeal) are also frequently involved and may abscessate. Retropharyngeal lymph nodes may drain into and cause empyema of the guttural pouch. Natural draining of these deeper abscesses to the skin may take several days or weeks, and the swelling can exert pressure on the pharynx, larynx, trachea, and esophagus, causing severe dyspnea, stridor, and dysphagia. Retropharyngeal lymph node abscessation is not always associated with swelling that can be appreciated externally. Periorbital abscesses can cause marked swelling of the eyelids. Abscesses of the lymph nodes at the thoracic inlet can cause severe tracheal compression, asphyxia, and death. Coughing is not a significant feature in many cases, although some horses develop a soft, moist cough that becomes more productive and increasingly

From the University of Pennsylvania, New Bolton Center, Kennett Square, PA (Sweeney); the University of Kentucky, Gluck Research Center, Lexington, KY (Timoney); Animal Health Trust, Newmarket, UK (Newton); and Washington State University, Pullman, WA (Hines).

This consensus statement has been approved by each author. Each author listed has contributed to the intellectual content of this statement and agrees with all interpretations and conclusions. None of the authors have any financial interest with companies that manufacture products or provide diagnostic services that are the subject of this paper. One of the authors (Timoney) shares a patent on the SeM sequence and its use (US Patent # 6,458,358 Oct. 1, 2002).

Copyright © 2005 by the American College of Veterinary Internal Medicine

0891-6640/05/1901-0021/\$3.00/0

severe as the disease progresses. Squeezing the larynx will often cause marked pain, stridor, and gagging followed by a retching cough and extended neck position when the neck is released. Expulsion of large quantities of pus from the nose or mouth with coughing usually indicates empyema of the guttural pouch.

Manifestations Associated with Severe Lymph Node Enlargement

Abscessation, particularly of the retropharyngeal lymph nodes, may result in obstruction of the upper respiratory tract. The enlarged lymph nodes may compress the pharynx, larynx, or trachea, necessitating a tracheostomy in severe cases. Temporary laryngeal hemiplegia, resulting from damage to the recurrent laryngeal nerve from enlargement of either the retropharyngeal or anterior cervical lymph nodes, may also contribute to dyspnea. Four of 15 horses with complicated strangles had upper respiratory tract obstruction requiring tracheostomy, and death was attributed to the obstruction in 2 of these.¹ Dysphagia may also occur as a result of lymph node enlargement or guttural pouch empyema.

Pathogenesis

S equi enters via the mouth or nose and attaches to cells in the crypt of the lingual and palatine tonsils and to the follicular-associated epithelium of the pharyngeal and tubal tonsils. There is no evidence for colonization prior to penetration but rather the organism reaches the deeper tissues of the tonsil within a few hours. Ligands responsible for binding may include the exposed surface proteins SzPSe, Se73.9, and Se51.9. FNZ, a fibronectin binding protein produced by *S zooepidemicus*, is also produced by *S equi* but without a C terminal anchor and so it may not be functional.² A few hours after infection, the organism is difficult to detect on the mucosal surface but is visible within cells of the epithelium and subepithelial follicles. Translocation occurs in a few hours to the mandibular and supratharyngeal lymph nodes that drain the pharyngeal and tonsillar region.

Complement-derived chemotactic factors generated after interaction of complement with bacterial peptidoglycan attract large numbers of polymorphonuclear neutrophils, although gross evidence of abscessation is not visible for 3 to 5 days after *S equi* enter the lymph node.³ Failure of neutrophils to phagocytose and kill the streptococci appears to be due to a combination of the hyaluronic acid capsule, antiphagocytic SeM protein, Mac protein, and other undertermined antiphagocytic factors released by the organism. This culminates in accumulation of many extracellular streptococci in the form of long chains surrounded by large numbers of degenerating neutrophils. Final disposal of bacteria is dependent on lysis of the abscess capsule and evacuation of its contents.

Streptolysin S and streptokinase may also contribute to abscess development and lysis by damaging cell membranes and activating the proteolytic properties of plasminogen. Although strangles predominantly involves the upper airways, including the guttural pouches and associated lymph nodes, metastasis to other locations occasionally occurs. Spread may be hematogenous or via lymphatic chan-

nels, which results in abscesses in lymph nodes and other organs of the thorax and abdomen. This form of the disease has been known as "bastard strangles." Metastasis to the brain has also been recorded.⁴ Bacteremia occurs on days 6 to 12 in horses inoculated intranasally with virulent *S equi*.⁵

The first clinical sign of infection is a rapid increase in rectal temperature to 103°F or higher. This occurs between 3 and 14 days after exposure and is associated with release of the pyrogenic mitogens SePE-H and I. Blood fibrinogen concentrations and white blood cell and neutrophil counts also increase. Abscess development is rapid and is often accompanied by lymph accumulation in afferent lymphatics.

Nasal shedding of *S equi* usually begins 2 to 3 days after onset of fever and persists for 2 to 3 weeks in most animals. Some animals never shed. In others, shedding may persist much longer should infection persist in the guttural pouch.^{6,7} Systemic and mucosal immune responses are evident 2 to 3 weeks after infection and coincide with mucosal clearance.⁸

The infectious dose of organisms propagated in media is probably much higher than is required during natural transmission because virulence factors essential for initial attachment and penetration are more likely to be expressed on in vivo-propagated bacteria. Also, the larger the intranasal inoculum of cultured *S equi*, the shorter the incubation period and the more severe the disease that results (JFT). Inocula of less than 10⁶ CFU are not consistently effective in causing disease because such low numbers of bacteria may be efficiently removed by mucociliary clearance.

Approximately 75% of horses develop a solid, enduring immunity to strangles after recovery from the disease.^{9,10} Horses in the immediate convalescent phase are resistant to experimental challenge with numbers of *S equi* greatly exceeding those required to produce the original infection.⁸ A small percentage of these horses become susceptible to a second attack of the disease within several months, which probably represents a failure to produce or maintain an adequate concentration of the relevant mucosal and systemic antibodies. Strong serum IgGb responses to surface-exposed proteins, including SeM, Se44.2, Se46.8, Se45.5, and Se42.0, are produced during convalescence. Opsonophagocytic serum IgGb specific for the highly antiphagocytic and immunogenic SeM appears late in convalescence in some but not in all horses.¹¹ In addition, SeM-specific IgGa is induced during and shortly after *S equi* infection. Strong SeM-specific mucosal IgA and IgGb responses occur during the acute and convalescent phases but not following intramuscular vaccination with M-like protein (SeM).¹² Older horses with residual immunity have limited susceptibility and develop a mild form of strangles often termed "catarrhal strangles." These animals shed virulent *S equi* that will produce severe disease in more susceptible, often younger horses.

Milk from mares that have recovered from strangles contains IgGb and IgA with specificities similar to those found in nasopharyngeal mucus of convalescent horses.¹³ Suckling foals therefore benefit from the protective effects of this antibody until weaned. Colostral antibodies ingested during the first 24 hours of life recirculate to the nasopha-

ryngeal mucosa, thus providing an additional source of protection to the foal during its first weeks. Foals that suckle immune mares are usually resistant to *S equi* infection until weaning.

Aspects of Pathogenesis Important in Control and Prevention

- Shedding does not begin until a day or two after onset of pyrexia. New cases can therefore be isolated before they transmit infection.
- Nasal shedding persists for 2 to 3 weeks in most animals. Persistent guttural pouch infection may result in intermittent shedding for years.
- Field and experimental data support the conclusion that disease severity is dependent on challenge load and duration.

Epidemiology

Transmission

Purulent discharges from horses with active and recovering strangles are an important and easily recognizable source of new *S equi* infections among susceptible horses. Transmission of infection occurs when there is either direct or indirect transfer of *S equi* within these purulent discharges between affected and susceptible horses. Direct transmission refers to horse-to-horse contacts, particularly through normal equine social behavior involving mutual head contact. Indirect transmission occurs through the sharing of contaminated housing, water sources, feed or feeding utensils, twitches, tack, and other less obvious fomites such as the clothing and equipment of handlers, caretakers, farriers, and veterinarians unless appropriate barrier precautions are undertaken to prevent spread of *S equi*.

It is increasingly recognized that there may be transmission that originates from outwardly healthy animals and in this situation the source of infection may not be readily recognized and clinical signs may appear in in-contact animals unexpectedly. *S equi* may originate from outwardly healthy horses that are incubating the disease and go on to develop disease. It is assumed that normal nasal secretions are the source of infection in these animals.

Apparently healthy horses recovering from recent disease might continue to harbor the organism after full clinical recovery. There is evidence that a moderate proportion of horses continue to harbor *S equi* for several weeks after clinical signs have disappeared, even though the organism is no longer detectable in the majority 4 to 6 weeks after total recovery. A recovered horse may be a potential source of infection for at least 6 weeks after its clinical signs of strangles have resolved.

Other horses are fully recovered from the disease but continue to be infectious for prolonged periods through periodic shedding of *S equi*. These horses are referred to as long-term, subclinical *S equi* carriers and can be a source of infection for susceptible animals. Their introduction to herds may be a source of new outbreaks, even in well-managed groups of horses. The efficacy of control for strangles must include recognition of this category of animal and adoption of appropriate methods for detection and

treatment. The best-recognized site of prolonged carriage of *S equi* among subclinical long-term carriers is the guttural pouch, which is known to become infected in the early phases of infection and following rupture of the adjacent retropharyngeal lymph nodes through the floor of the pouch. It is likely that short-lived guttural pouch empyema is the most frequent outcome of uncomplicated drainage of retropharyngeal lymph node abscessation. The carrier state develops in up to 10% of affected animals, resulting in chronic empyema of the pouches. Should the purulent material persist in the guttural pouch, it can become inspissated and eventually form into discrete masses known as "chondroids." Chondroids may occur singly or as multiples, sometimes in very large numbers. Chondroids formed after strangles can harbor *S equi*, based on cultures of chondroids removed from these animals and demonstrated histologically on the surface and lining fissures within their structure (JRN). In some animals, guttural pouch empyema with *S equi* infection may persist asymptotically for many months or even years. About 50% of horses with guttural pouch empyema cough sporadically and some may have an intermittent unilateral nasal discharge.

Environmental Persistence of *S equi*

Currently there is a lack of field-based proof for prolonged environmental persistence of *S equi*. One laboratory-based study¹⁴ documented that the organism in the form of a smeared laboratory grown bacterial suspension survived for 63 days on wood at 2°C and for 48 days on glass or wood at 20°C. This study did not include coinfection with other normal environmental bacterial flora. *S equi* is sensitive to bacteriocins from environmental bacteria and does not readily survive in the presence of other soil-borne flora. Hence, the authors suggest that the results from the Jorm study as they apply to field conditions should be interpreted with caution. Further studies to evaluate the environmental persistence of *S equi* in clinical samples (eg, purulent discharges from cases of strangles) under field rather than laboratory conditions are warranted.

Diagnosis

Culture

Culture of nasal swabs, nasal washes, or pus aspirated from abscesses remains the "gold standard" for detection of *S equi*. Specimens should be plated on Columbia CNA (colistin, nalidixic acid) agar with 5% sheep or horse blood added. The presence of other beta hemolytic streptococci, especially *S zooepidemicus*, may complicate interpretation of cultures. Colonies of virulent *S equi* are always mucoid, whereas those of the attenuated live vaccine available in North America are small and dry. Colonies of commensal *S zooepidemicus* are also typically nonmucoid, whereas fresh isolates from invasive infections are often mucoid. Unlike *S equi*, *S zooepidemicus* ferments sorbitol and lactose.

Nasal washes are more effective than swabs in detection of small numbers of *S equi* because a greater surface area within the internal nares is sampled. The technique involves instilling about 50 mL of warm normal saline via a 15-cm

length of soft rubber tubing (5–6 mm diameter) inserted to the level of the nasal canthus and collecting the washings^{13,15} These washings are centrifuged, and the pellet cultured. Culture may, however, be unsuccessful during the incubation and early clinical phases. *S equi* is normally not present on the mucosa until 24 to 48 hours after the onset of fever, and so horses monitored by daily measuring of rectal temperatures during an outbreak may be recognized early and isolated to limit transmission of *S equi*.

PCR

The polymerase chain reaction (PCR) is designed to detect DNA sequence of SeM, the gene for the antiphagocytic M protein of *S equi*. Although an allele of this gene is found in some strains of *S zooepidemicus*, much of the sequence is of low homology and primer sequences designed from SeM will not prime synthesis of an amplicon from *S zooepidemicus*. There is also no evidence that an SeM-like protein is expressed by *S zooepidemicus*. The PCR based on SeM therefore offers an adjunct to culture for detection of *S equi*.¹⁶ Because the test can be completed in a few hours, results may be available on the same day that samples are taken. However, PCR does not distinguish between dead and live organisms and so a positive test result must be considered presumptive until confirmed by culture. In addition, clinical samples that contain polymerase inhibitors or abundant *S equi* may give negative PCR results, although culture of the same sample confirms the presence of *S equi*. PCR is approximately 3 times more sensitive than culture.^{15,17}

PCR accompanying culture of a nasal swab or wash may be used in a control program to select animals for guttural pouch endoscopy.¹⁷ PCR is capable of detecting SeM DNA of *S equi* for weeks in guttural pouch lavages following disappearance of live organisms. This is not the case for the nasopharynx, where the efficient mucociliary apparatus removes organisms and DNA at the same time.

PCR is useful to:

- Detect asymptomatic carriers.
- Establish *S equi* infection status prior to transport.
- Establish *S equi* infection status following transport prior to commingling.
- Determine the success of elimination of *S equi* from the guttural pouch.

Serology

Fifteen or more surface-exposed or -secreted proteins of *S equi* elicit strong serum antibody responses during infection and convalescence. The most reactive and best studied of these is SeM, a major virulence factor and protective immunogen.¹⁸ A proprietary ELISA for measuring SeM-specific antibody is commercially available^a and is useful for diagnosing recent (but not necessarily current) *S equi* infection, determining the need for booster vaccination, and as an aid in the diagnosis of purpura hemorrhagica and metastatic abscesses. It does not distinguish between vaccine and infection response. Comparison of titers obtained from sequential samples may provide an indication of exposure and infection status. Serum titers peak about 5

weeks after exposure and remain high for at least 6 months.¹² Responses to commercial extract vaccines peak at about 2 weeks and remain high for 6 months.¹²

Considerable variation in the responses of individual horses should be kept in mind when interpreting results of measurement of SeM-specific antibody. Horses at risk for development of purpura are hyperresponders and make very strong antibody responses. Such animals, with titers in excess of 1:3200, should never be vaccinated (JFT).

Interpretation of SeM-specific ELISA

Negative

No SeM-specific antibodies detected. This result may occur in a horse with no previous exposure to *S equi* or vaccine or exposure to *S equi* may be recent (<7 days).

Weak Positive (1:200–1:400)

SeM-specific antibodies detected at a very low level. This is an equivocal result and may represent very recent or residual antibody from exposure to *S equi* or vaccine in the remote past. Repeat testing is recommended in 7 to 14 days to confirm recent exposure.

Moderate Positive (1:800–1:1,600)

SeM-specific antibodies detected at an intermediate level. This level may occur in a horse at 2 to 3 weeks after exposure or where the infection occurred 6 months to 2 years previously.

High Positive (1:3,200–1:6,400)

SeM-specific antibodies detected at a high level. High levels are found from 4 to 12 weeks after infection or following vaccination: 1 to 2 weeks with the injectable form or 2 to 4 weeks with the intranasal form. Vaccination is contraindicated in horses with existing high levels of antibody (>1:1,600).

Very High Positive (>1:12,800)

SeM-specific antibodies detected at a very high level. These levels are often found in horses with a metastatic abscess or purpura hemorrhagica (immune-mediated vasculitis) following exposure to strangles vaccine or *S equi*.

The SeM-specific ELISA is useful to:

- Detect recent infection.
- Determine need for vaccination.
- Identify animals with existing high levels of antibody that might predispose to purpura hemorrhagica.
- Support a diagnosis of existing *S equi*-associated purpura hemorrhagica.
- Support diagnosis of bastard strangles.

Vaccination

Most horses develop a solid immunity during recovery from strangles, which persists in over 75% of animals for 5 years or longer.^{9,10} This indicates that stimulation of a high level of immunity is biologically feasible given appropriate presentation of protective immunogen(s). *S zooepidemicus*,

although closely related to the clonal *S equi*, does not stimulate immunity that is cross-protective¹⁹ and so recent and current research on protective immunity is heavily focused on identifying immunogens expressed by *S equi* but absent from *S zooepidemicus*. The basis of acquired resistance to strangles is not completely understood but is believed to reside in part in antibodies to SeM and other immunogens unique to *S equi*. Early studies in Australia suggested that the protective immunogens are sensitive to temperature in excess of 56°C.²⁰ There is evidence that immunity in horses resistant to reinfection is mediated at the mucosal level and functions to block entry of *S equi*. However, systemic immunity following parenteral inoculation of avirulent live *S equi* is also protective. Together, these findings indicate that optimum immunity may require both systemic and mucosal responses.

Earlier bacterin-type vaccines have been superseded (North America and Australia) by adjuvanted extracts of *S equi* prepared by hot acid or by mutanolysin plus detergent extraction. Hot acid cleaves and removes acid-resistant proteins and carbohydrate mutanolysin (muramidase) hydrolyses the bacterial cell wall, releasing intact surface proteins in the presence of detergent. Both types of vaccine are potent and contain the immunogenic SeM. However, the efficacy of extract vaccines has been disappointing, with little published data to support significant protection. One study suggested a reduction in the clinical attack rate of 50% in vaccinates a few weeks following the final booster.²¹ Adverse reactions include soreness or abscesses at injection sites and occasional cases of purpura hemorrhagica.

An attenuated, nonencapsulated strain of *S equi* with defects in carbohydrate utilization and designed to mimic the immunity stimulated by natural infection stimulated a high level of immunity against experimental challenge.¹⁵

The inductive sites are the pharyngeal and lingual tonsils and so vaccine organisms must reach these sites in sufficient numbers to trigger protective responses. Safety issues include residual virulence with formation of slowly developing mandibular abscesses in a small percentage of vaccinates, nasal discharge, and occasional cases of immune-mediated vasculitis (purpura). Because the vaccine contains live *S equi*, accidental contamination of remote injection sites will result in abscess formation at these locations. For that reason, ideally no other vaccinations are given concurrently or are administered prior to the administration of the intranasal vaccine. No data are available to comment on the effect of concurrently administering a different intranasal vaccine. The genetic stability of the vaccine has recently been improved by deletion of portions of 2 genes (*HasA* and *B*) required for capsule synthesis. The deletion has also provided a reliable means of identifying the vaccine from wild strains using colony characteristics and PCR.

It is likely that more effective and safer vaccines will eventually be developed based on genomic sequence information from *S equi* and *S zooepidemicus*. However, the magnitude of this task is considerable. Protective immunogens must be identified for systemic and mucosal responses and the appropriate modes of presentation elucidated by experiment. Because it is likely that different immunogens function at the tonsillar and lymphatic levels, the

appropriate combination of these components will also have to be identified in multiple experiments with ponies/horses.

Extract Vaccines

Extract vaccines are given intramuscularly or subcutaneously and elicit serum antibody responses 7 to 10 days later. Naïve horses and foals require a schedule of 2 or 3 doses at an interval of 2 weeks. Booster doses are given once annually. Pregnant mares may be boosted a month before expected date of foaling. Horses known to have had strangles within the previous year should not be vaccinated. Horses with signs of strangles should not be vaccinated. During an outbreak, only horses with no known direct contact with strangles cases or the exudates from these cases should be promptly vaccinated. No published data show that vaccination with the avirulent, nonencapsulated strain Pinnacle[™] in the face of exposure is detrimental. However, development of immunity following vaccination takes ~2 weeks. Additionally, there is a real risk of transmitting the virulent, wild *S equi* to other horses as they are vaccinated.

S equi-specific serum antibody levels of valuable horses could be assayed prior to decision to vaccinate. Animals with titers of 1:1,600 or greater in the SeM ELISA should not be vaccinated (JFT).

Attenuated Live Intranasal Vaccine

Live vaccine should be administered only to healthy, nonfebrile animals free of nasal discharges. Vaccine is given in a schedule of 2 doses at 2- to 3-week intervals. Annual booster doses are recommended. Live vaccine should not be used during an outbreak except in horses with no known contact with infected or exposed animals. The mode of application should be such that an adequate amount of vaccine reaches the pharyngeal and lingual tonsils.

Transfer of passive immunity to the foal mainly involves antibodies of the IgGb isotype, which are distributed to the serum and nasal secretions. Parturition vaccination of the mare significantly increases colostral levels of these antibodies. Foals from vaccinated mares have significantly higher titers of SeM-specific IgGb but not IgA in mucosal washes during the first 2 months of life, although colostral levels of SeM-specific IgA are significantly increased by vaccination. Resistance of the foal to strangles during the first months of life appears to be mediated by IgGb in mucosal secretions and milk and not by IgA. No data are available about colostral antibody levels following administration of the intranasal vaccine administered to broodmares.

Control of Outbreaks

Outbreak Investigations

Investigation of strangles outbreaks should begin by an interview with horse owners to obtain a detailed history and to evaluate the potential full extent of the disease problem. The review should identify affected groups of horses and allow the geography of the premises and the management practices to be assessed for further risks and future opportunities for disease control.

A practical disease control strategy should then be agreed and implemented. The general aims and measures for such

Table 1. Aims and associated measures used to control transmission of *S equi* on affected premises.

Aim	Measure
To prevent the spread of <i>S equi</i> infection to horses on other premises and to new arrivals on the affected premises.	Stop all movement of horses on and off the affected premises immediately and until further notice. Horses with strangles and their contacts should be maintained in well-demarcated “dirty” (ie, <i>S equi</i> positive) quarantine areas. Clustering of cases in groups should allow parts of the premises to be easily allocated as “dirty” and “clean” areas.
To establish whether convalescing horses are infectious after clinical recovery.	At least 3 nasopharyngeal swabs or lavages are taken at approximately weekly intervals from all recovered cases and their contacts and tested for <i>S equi</i> by culture and PCR. Horses that are consistently negative are returned to the “clean” area.
To investigate all outwardly healthy horses in which <i>S equi</i> is detected either by culture or PCR.	Endoscopy of the upper respiratory tract and guttural pouches.
To eliminate <i>S equi</i> infection from the guttural pouches.	Healing of lesions through a combination of flushing and aspiration with saline and removal of chondroids using endoscopically guided instruments. Topical and systemic administration of antimicrobials to eliminate <i>S equi</i> infection.
To prevent indirect cross-infection by <i>S equi</i> from horses in the “dirty” area to those in the “clean” area of the premises.	Personnel should use dedicated protective clothing when dealing with infectious animals and should not deal simultaneously with susceptible animals. If this is unavoidable, infectious horses should be dealt with after susceptible animals. Strict hygiene measures are introduced, including provision of dedicated clothing and equipment for each area, disinfection facilities for personnel, and thorough stable cleaning and disinfection methods. When cost is not a factor, consideration should be given to destruction of this equipment following eradication of the infection. Following removal of organic material from stables, all surfaces should be thoroughly soaked in an appropriate liquid disinfectant or steam treated and allowed to dry. This should be repeated if possible. Manure and waste feed from infectious animals should be composted (inactivation of bacteria by heat) in an isolated location. Pastures used to hold infectious animals should be rested for 4 weeks. Care should be taken to disinfect water troughs at least once daily during an outbreak. Horse vans should be hosed clean and disinfected after each use.

a strategy are outlined in Table 1. This outline strategy may need to be adapted to the individual circumstances of specific premises and outbreaks. In summary:

- All movements of horses on and off the affected premises should be stopped and segregation and hygiene measures implemented immediately.
- Cases of strangles and their contacts should be maintained in well-demarcated “dirty” (ie, *S equi* positive) quarantine areas.
- Rectal temperatures should be taken at least once daily during an outbreak to detect, promptly segregate, and possibly treat new cases.
- The aim of the control strategy, following bacteriological screening, is to move horses from the “dirty” to “clean” areas where nonaffected and noninfectious horses are kept.
- Every care should be taken to ensure very high hygiene standards throughout the premises and for the duration of the outbreaks.
- Screening of all convalescing cases following clinical recovery and their healthy contacts should be conducted using swab or lavage of the nasopharynx, with special care taken to maintain good hygiene to avoid inadvertent transmission between horses during sampling.
- Swabs or lavage fluid should be collected at weekly in-

tervals following recovery over several weeks and tested for *S equi* by conventional culture and PCR.

- Because PCR can detect dead as well as living bacteria, positive PCR results are regarded as provisional, subject to further investigation.
- Because the vast majority of subclinical long-term carriage of *S equi* appears to occur in the guttural pouches of recovered horses, endoscopy of the upper respiratory tract and guttural pouches should be performed in all outwardly healthy horses in which *S equi* is detected, either by culture or by PCR.
- Lavage samples from guttural pouches should then be tested for *S equi* by culture and PCR.
- Sites such as the cranial nasal sinuses or tonsils should be considered in horses that continue to harbor *S equi* in the absence of pathology or *S equi* infection of the guttural pouches.

Detection of Carriers with *S equi* Infection of the Guttural Pouches

Diagnosis of *S equi* infection associated with guttural pouch empyema with or without chondroids following strangles is best achieved by direct visual assessment of both pouches using endoscopy. Cytological assessment and culture and PCR for detection of *S equi* in lavage samples

collected via a sterile disposable catheter passed through the biopsy channel of the endoscope are recommended to accompany visual examination because infection and inflammation may be present in the absence of obvious and visible pathology. Diagnosis of guttural pouch empyema with or without chondroids may also be made by radiography of guttural pouch area, although changes may not be visible in all cases.

S equi may be cultured from lavages collected by direct percutaneous sampling of the pouch, although this is not recommended because of the high risk of injury to important anatomical structures in the region.

Treatment of Carriers with *S equi* Infection of the Guttural Pouches

Appropriate methods of treatment of guttural pouch empyema in individual horses depend on the consistency and volume of the material within the pouches. Repeated lavages of pus-filled pouches via rigid or indwelling catheters using isotonic saline or polyionic fluid and with subsequent lowering of the head to allow drainage or use of a suction pump attached to the endoscope aid the elimination of empyema. Sedation aids in implementation of the endoscopy and facilitates drainage of flush material from the guttural pouches by lowering the horse's head.

Administration of both topical and systemic benzylpenicillin appears to improve treatment success rate. Verheyen et al²² report on the method of delivering a gelatin/penicillin mix. To make 50-mL gelatin/penicillin solution:

- Weigh out 2 grams of gelatin (Sigma G-6650 or household grade) and add 40 mL sterile water.
- Heat or microwave to dissolve the gelatin.
- Cool gelatin to 45–50°C.
- Meanwhile add 10 mL sterile water to 10,000,000 units (10 Mega) sodium benzylpenicillin G.
- Mix penicillin solution with the cooled gelatin to make a total volume of 50 mL.
- Dispense into syringes and leave overnight at 4°C to set.

The gelatin-penicillin mix is more effective in remaining in the pouches than a straight aqueous solution and is a useful way of delivering a large dose of penicillin where it is needed. Installation is easiest through a catheter inserted up the nose and endoscopically guided into the pouch opening. The catheter works best with the last 1 inch bent at an angle to aid entry under the pouch flap. Recommendations include elevating the horse's head after infusion.

Topical installation of 20% (w/v) acetylcysteine solution has also been used to aid the treatment of empyema. Acetylcysteine has a denaturing and solubilizing activity by disrupting disulphide bonds in mucoprotein molecules, thus reducing mucus viscosity and so theoretically facilitating natural drainage. Erythema of the mucus membranes lining the guttural pouch has been observed following installation of 20% (w/v) acetylcysteine solution. More long-standing cases, in which there is inspissation of the purulent material that does not readily drain into the pharynx, are more difficult to treat topically because they can be refractory to large volume irrigation. Use of a memory-helical polyp retrieval basket through the biopsy channel of the endoscope

does allow nonsurgical removal of chondroids, even when present in very large numbers and in conjunction with empyema (JRN). When combined with topical and systemic antimicrobial treatment, this is usually sufficient for cure of severe guttural pouch lesions. Surgical hyovertebroto-my and ventral drainage through Viborg's triangle carries inherent risks of general anesthesia and surgical dissection around major blood vessels and nerve and *S equi* contamination of the hospital environment. Scarring of the pharyngeal openings of the guttural pouch may preclude both natural drainage of purulent material and endoscopic access to the guttural pouches. Such cases may require conventional surgical or endoscopically guided laser treatments to break down scar tissue and allow access to the pouches.

Hygiene Measures

Particular care should be taken with hygiene measures during strangles outbreaks to prevent indirect transfer of *S equi* from infectious horses (including potential subclinical carriers) to susceptible animals. Personnel should use dedicated protective clothing when dealing with infectious animals and should not deal simultaneously with susceptible animals. If this is unavoidable, infectious horses should be dealt with after susceptible animals. Only dedicated equipment should be used for infectious horses; the equipment should be thoroughly disinfected between animals. When cost is not a factor, consideration should be given to destruction of the equipment following eradication of the infection. When disinfecting stables used by infectious horses, care should be taken to ensure thorough cleaning to remove all organic material. Particular care must be taken with feed and water troughs as well as wooden fencing or other wooden surfaces. Manure and waste feed from infectious animals should be composted in an isolated location. Personnel dealing with susceptible animals should avoid contact with waste from infectious horses. Following removal of organic material from stables, all surfaces should be thoroughly soaked in an appropriate liquid disinfectant or steam treated and allowed to dry. This should be repeated if possible. Care should be taken with wooden surfaces. Following thorough cleaning and soaking in liquid disinfectant, they should be treated with suitable wood preservative or sealed with epoxy paint. Pastures used to hold infectious animals should be rested for 4 weeks. There is no evidence for prolonged survival of *S equi* on pastures. Care should be taken to disinfect water troughs at least once daily during an outbreak. Horse vans should be hosed clean and disinfected after each use.

S equi does not present any more problems with disinfection of equipment than do any other bacterial species, and normal, commonsense approaches should be adopted at all times. This should include ensuring physical removal of visible organic material and use of an appropriate disinfectant that is proven to act against *S equi* using appropriate manufacturer guidelines on dilution.

Cases of *S equi* infection in debilitated humans have been reported. Animal handlers, caretakers, veterinary practitioners, pathologists, and equine postmortem attendants should take particular care to avoid unnecessary contamination from infectious horses, especially avoiding respiratory and

oral contamination by purulent material. It should, however, be remembered that *S equi* is highly host adapted and infections of humans have rarely been confirmed.

Prevention

Quarantine/bacteriological screening

- Prevention of strangles through quarantining and screening is difficult to achieve, especially without specific measures to reduce the risk of inadvertent introduction of *S equi* infection through subclinical carriers. The owner/farm managers/trainer should always be questioned as to the possible exposure of the animal to strangles.
- Prevention through quarantining and screening is particularly difficult where there is frequent moving and mixing of horses during the breeding season and at race-tracks and where strangles outbreaks have not been appropriately investigated and controlled.
- Wherever possible, animals being introduced to a new population of horses should be isolated for 3 weeks and screened for *S equi* by repeated nasopharyngeal swabs or lavages.
- This should be done in accordance with the protocol outlined for controlling outbreaks (ie, 3 samples taken at weekly intervals), with samples tested for *S equi* by culture and PCR and animals testing positive being retained in isolation for further investigation and treatment.
- High standards of hygiene should also always be maintained to avoid indirect transmission between quarantined and resident horses.

The Horserace Betting Levy Board in the United Kingdom has established guidelines on strangles included in its Codes of Practice, which can be viewed at the following Web address: <http://www.hblb.org.uk/hblbweb.nsf/Codes%20of%20Practice%202004.pdf>.

Treatment

Appropriate treatment of horses with strangles usually depends on the stage and severity of the disease. Veterinary opinion as to whether or not to use antibiotic treatment remains markedly divided. However, the majority of strangles cases require no treatment other than proper rest and a dry, warm stall and provision of soft, moist, and palatable food of good quality while letting the disease run its course. Food and water should be easily accessible to the horse.

Horses with Early Clinical Signs

During an outbreak, immediate antibiotic therapy of new cases in the early acute phase with fever and depression may be curative and may prevent focal abscessation. Antibiotics should be given for 3 to 5 days. However, treated animals are likely to remain susceptible to reinfection. Experimental infected ponies treated with antibiotics at onset of fever usually do not develop lymph node abscessation if protected from further exposure. Because abscesses have not developed at this early stage, the antibiotics have adequate access to the bacteria.

Unfortunately, antibiotic treatment will also inhibit synthesis of protective antigens and the development of pro-

TECTIVE immunity will not be stimulated from strangles,²³ so the horses will be highly susceptible to reinfection once treatment is discontinued if the horse remains exposed to infected horses.

It has been argued on theoretical grounds that treatment of strangles with antibiotics is contraindicated because killing the organisms is indirectly affecting the development of immunity and thereby increasing the risk of bacteremia, septicemia, and metastatic abscessation. There are no experimental or clinical data to support such a phenomenon. Immediate treatment of horses that show the earliest clinical sign of fever could be an effective way of controlling strangles outbreaks in racing stables or riding barns, although the disadvantages of treatment just discussed should be weighed.

Horses with Lymph Node Abscessation

Once an external lymphadenopathy is detected in an otherwise alert and healthy horse, antibiotic therapy is probably contraindicated. Although it provides temporary clinical improvement in fever and lethargy, it only prolongs the inevitable enlargement and eventual rupture of lymph node abscess. Antibiotics may suppress the bacteria within the lymph nodes sufficiently for a time, only to have a simmering infection flare and abscessation return when the antibiotics are discontinued.

Therapy should be directed toward enhancing maturation and drainage of the abscesses. Topical treatments such as ichthamol or a hot pack may be applied to promote maturation of the lymph node abscess, although objective, controlled data supporting the use of these techniques are lacking. Surgical drainage of lymphadenopathies is sometimes indicated if abscesses do not rupture spontaneously; however, it is critical to wait until the abscess has matured and thinned out ventrally. Earlier, surgical intervention may only result in minimal exudate drainage and continued lymph node swelling, because the abscess has enough internal structure (honeycomb loculations) to block drainage through a single surgical incision. Daily flushing of the open abscess with a 3–5% povidone iodine solution should be continued until the discharge ceases.

The use of nonsteroidal anti-inflammatory medications such as phenylbutazone or flunixin meglumine may improve the horse's demeanor by reducing fever, pain, and inflammatory swelling at the site of the abscesses. This may in turn encourage eating and drinking. Consideration must be given to the complications seen following the use of nonsteroidal anti-inflammatory medications in dehydrated and anorectic horses.

Even in the face of detectable lymphadenopathy, if the horse is febrile, depressed, anorexic, and especially manifesting dyspnea as result of partial upper airway obstruction, antibiotic therapy is indicated to decrease abscess size and prevent complete airway obstruction. Rarely, affected horses may require intensive supportive therapy, including intravenous fluids, feeding by nasogastric tube, and tracheostomy. An animal requiring a tracheostomy should be given systemic antimicrobial drugs to prevent secondary bacterial infections of the lower respiratory tract.

Some clinicians believe that antibiotic therapy after ab-

cesses have ruptured is indicated because it may hasten recovery, improve appetite, and reduce loss of body condition.

Horses with Complications

Horses that develop complications from strangles should receive symptomatic therapy. This will be discussed under complications.

Drugs of Choice for Therapy

Penicillin is generally considered the drug of choice for the treatment of nonpneumococcal streptococcal disease, with alternative drugs used depending on ease of administration or the site of infection. Other agents for therapy include cephalosporins and macrolides. Based on in vitro antimicrobial susceptibility testing where testing methods follow the Clinical and Laboratory Standards Institute's guidelines, the majority of *S equi* isolates are susceptible to trimethoprim-sulfadiazine (TMS). However, this may or may not translate into in vivo efficacy. Many veterinarians have anecdotally indicated that horses with strangles have improved with TMS treatment. Although there is evidence that TMS did not eliminate *S zooepidemicus* infection in tissue chambers implanted subcutaneously in ponies, the study did not determine its effectiveness against *S equi*.²⁴

S equi is consistently sensitive to penicillin; thus it is considered the antibiotic of choice. Laboratories (personal communications: JFT and JRN) handling hundreds of *S equi* strains have noted no emerging antibiotic resistance to penicillin by *S equi* or *S zooepidemicus*. The incidence of resistance to most other drugs is low with the exception of aminoglycoside resistance, including gentamicin, which is consistently observed.

Complications Associated with *S equi* Infection

The overall complication rate associated with *S equi* infection is approximately 20%.^{1,25} The occurrence of complications can significantly increase the case fatality rate. In a study in which data were collected from a 235-horse farm, 74 horses had strangles, 15 of which (20.3%) had complications.¹ Of those horses with complications, the outcome was either death or euthanasia in 40%, compared with an overall case fatality rate of 8.1%.

A variety of complications can occur as a result of strangles. These can be generally grouped as:

- Those associated with the spread of infection from the head and neck region to other locations.
- Immune-mediated processes, including purpura hemorrhagica and myopathies.
- Agalactia.

Complications Associated with Metastatic Spread of Infection

S equi may potentially infect any anatomic site. The term *bastard strangles* is often used to describe metastatic abscessation. Spread of the organism may occur through several routes, including hematogenous spread, lymphatic migration, or via close association with a septic focus, for

example, when connecting structures, such as cranial nerves, allows transport of the organism or when there is direct aspiration of purulent material.

Common sites of infection include the lung, mesentery, liver, spleen, kidneys, and brain. Respiratory distress may occur due to tracheal compression resulting from enlargement of the cranial mediastinal lymph nodes. Suppurative bronchopneumonia is one important sequela of strangles. Of 15 horses with complications associated with strangles, 5 had pneumonia or pleuropneumonia, and 3 of 5 deaths were attributed to pneumonia, making this the most common complication resulting in death.^{1,26} In a previous study, 22 of 35 cases with complications (62%) died of pneumonia secondary to strangles.²⁵

Another important complication of strangles is extension of infection to the sinuses or guttural pouches. In a general study of guttural pouch empyema, *S equi* was isolated in 14 of 44 horses; 5 of 74 horses with strangles had guttural pouch involvement.^{1,26} Infection of the guttural pouch is of particular importance because the guttural pouch is the most common site for prolonged carriage of the organism.^{7,22} Horses with infection in the sinuses may also become carriers. Other reported conditions associated with *S equi* infection include myocarditis, endocarditis, panophthalmitis, periorbital abscesses, ulcerative keratitis, paravertebral abscesses, septic arthritis, and tenosynovitis.

The diagnosis and treatment of *S equi* infections that have spread are potentially more difficult than in cases of uncomplicated strangles. The specific means of diagnosis vary depending on the site of infection and whether there are concurrent signs of classic strangles. For infections such as bronchopneumonia, guttural pouch empyema, or sinusitis, appropriate samples can be collected for culture. However, for some internal abscesses, a specific diagnosis may be difficult. A history of exposure to *S equi* and laboratory results consistent with chronic infection, such as elevated SeM-specific antibody titers, anemia, low-grade fever responsive to penicillin, hyperfibrinogenemia, and hyperglobulinemia, are supportive of the diagnosis of metastatic abscessation. Mesenteric abscesses may be accompanied by an immune ascites with elevated SeM-specific antibody in ascitic fluid. Treatment of *S equi* infection that has spread frequently involves long-term antimicrobial therapy, and appropriate local treatment or drainage of abscesses if possible.

The prevalence of metastatic abscessation is generally low. However, in a recent study in which outbreaks of strangles on 2 farms were investigated, 7 out of 25 (28%) developed metastatic abscessation.⁴ Of these, euthanasia was performed in 5 horses, 4 of which had neurologic signs and confirmed cerebral abscesses. The reason for the high incidence of complications, and particularly neurologic disease, on these farms is unclear, but possible theories include a high infectious dose, the virulence of the strains involved, differences in host susceptibility, or other unidentified factors.

It has been suggested that antimicrobial treatment following the development of an abscess might contribute to metastasis, based on the theory that protein synthesis by the organism is altered by antimicrobial treatment and reduced immunogen level results in suboptimal immune response.

However, there are currently no experimental or clinical data that support the theory that antimicrobial treatment increases the prevalence of bastard strangles. In the study by Spoomakers et al,⁴ no antibiotics were used in any of the cases before complications were identified, yet the incidence of significant complications was high and it is known that metastatic infection has occurred in other outbreaks where antibiotics have not been used.

Immune-Mediated Complications

Purpura Hemorrhagica

Purpura hemorrhagica is an aseptic necrotizing vasculitis characterized primarily by edema and petechial or ecchymotic hemorrhage. Although the exact pathogenesis of purpura hemorrhagica is not fully understood, it appears to be a vasculitis caused by the deposition of immune complexes in blood vessel walls. Although commonly associated with *S equi* infection, purpura may also occur in response to a number of different antigens. Of 53 horses with purpura, 17 were exposed to or infected with *S equi* and 5 were vaccinated with *S equi* M protein, whereas the remaining 31 cases were either associated with other organisms or had no known causes.²⁷

The risk of developing purpura hemorrhagica following exposure to *S equi* through infection or vaccination is not known. Four of 74 horses with strangles developed purpura; all 4 were male yearlings that had been vaccinated with an M protein vaccine and all developed signs of purpura hemorrhagica within 2–6 days after the onset of strangles.¹ A pre-existing high serum antibody titer to *S equi* antigens may predispose horses to the development of purpura.

Studies have suggested an association between the development of purpura and antibodies of the IgA isotype. IgA titers to both M-like protein and culture supernatant proteins were higher in horses with purpura than in either horses recently infected with *S equi* or those with no known history of exposure.²⁸ In addition, a rise in the IgG antibody titer coincided with the onset of clinical recovery in horses with purpura. Immune complexes with IgA and M-like proteins have been found in the sera of horses with purpura.²⁹ The immunologic basis for the high concentrations of IgA and low concentrations of IgG during the acute stages of purpura is not understood. Some proposed explanations include uncontrolled expansion of B cell populations that produce IgA, failure of IgA removal mechanisms, delayed production of IgG in response to a novel stimulus, defective or suppressed production of IgG, and neutralization or excess utilization of IgG.

Clinical Signs and Diagnosis of Purpura Hemorrhagica

The severity of clinical signs seen with purpura varies from a mild, transient reaction to a severe, fatal disease.²⁷ The typical clinical signs seen as a result of the vasculitis include subcutaneous edema, most frequently involving the head, limbs, and/or trunk, and petechiation and ecchymoses of the mucous membranes. Severe edema may result in oozing from the skin surfaces, and sloughing of the skin may occur. In some cases, the vasculitis may affect other sites

such as the gastrointestinal tract, lungs, and muscle, resulting in signs such as colic, respiratory difficulties, and muscle soreness.

Leukocytoclastic vasculitis on histologic exam of skin is consistent with a diagnosis of purpura hemorrhagica. In those cases associated with *S equi*, isolation of the organism and demonstration of elevated IgA and IgG titers to *S equi* are also supportive.

Treatment and Prognosis of Purpura Hemorrhagica

Corticosteroids are the primary treatment for purpura. Generally, dexamethasone at 0.1–0.2 mg/kg followed by a tapering dose regime is used. In those cases where purpura is associated with active bacterial infection or the horse is considered at high risk of developing infection, appropriate antibiotic therapy is also indicated. Nonsteroidal anti-inflammatory drugs may be of some benefit in some cases of purpura. Supportive care, including intravenous fluids, hydrotherapy, and bandaging may also be indicated. The majority of the 53 horses with purpura were treated for more than 7 days.²⁷

Purpura hemorrhagica can be a serious complication of strangle. One of the 4 cases with purpura was euthanized due to the severity of the skin necrosis.¹ Similarly, 3 of 22 horses with purpura secondary to exposure to *S equi* did not survive.²⁷

Myositis

Two types of myopathies, muscle infarctions and rhabdomyolysis with progressive atrophy, have been documented in horses following exposure to *S equi*. These syndromes are both presumed to be immune-mediated, although through different mechanisms. Although the exact pathogenesis for either syndrome has not been fully elucidated, muscle infarction is thought to result from an immune-mediated vasculitis, whereas rhabdomyolysis with progressive atrophy is thought to result from cross-reactivity between SeM and myosin. In a study of 25 horses with either strangles or purpura, 8 had evidence of muscle abnormalities based on serum chemistries and/or histologic muscle lesions.³⁰ Four of these horses had muscle infarctions, and the other 4 had rhabdomyolysis.

Muscle Infarctions

This syndrome is most likely a manifestation of purpura hemorrhagica. Many horses with purpura exhibit mild elevations in serum creatine kinase (CK) activity due to vasculitis within the muscle and mild muscle necrosis. Titers of SeM-specific antibody may exceed 1 : 6,400. Some horses develop a severe vasculopathy characterized by infarction of skeletal muscle, skin, gastrointestinal tract, and lungs.³⁰ These horses present with muscle stiffness, lameness, and elevations in muscle enzymes in conjunction with other signs, such as abdominal pain and subcutaneous swelling. On histopathology, there is acute coagulative necrosis of muscle with infarctions. Also, pulmonary hemorrhage and gastrointestinal infarctions may be present.

Even with aggressive corticosteroid therapy and antibiotics, the prognosis is guarded.

Rhabdomyolysis with Progressive Atrophy

Significant rhabdomyolysis has been identified in some quarter horses following exposure to *S equi*.³⁰ Some of these horses had underlying polysaccharide storage myopathy and developed rhabdomyolysis while ill. Others developed myositis without an underlying problem and exhibited malaise and a rapidly progressive atrophy of the epaxial and gluteal muscles. Muscle enzymes were elevated and muscle biopsies revealed chronic active rhabdomyolysis with regeneration, prominent macrophage infiltration, atrophy of fast-twitch fibers, and lymphocytic vasculitis. Over time, fibrosis developed around blood vessels. The horses may or may not have concurrent signs of actual strangles. This syndrome may be an immune response resulting from similarities between the amino acid sequence of an *S equi* protein and equine myosin in certain horses. In humans with rheumatic fever, a sequela to *S pyogenes* infection, streptococcal antigens induce immune responses to epitopes in myocardial myosin.³⁰ The presence of IgG within the fast-twitch muscle fibers has been confirmed in 1 horse, further supporting an immune-mediated pathogenesis.³⁰ Affected horses should be treated with corticosteroids, and muscle mass may return to normal. If there are signs consistent with concurrent infection, antibiotics are also indicated.

Glomerulonephritis, Myocarditis

Streptococcal antigens have been suggested as a trigger for development of myocarditis and proliferative glomerulonephritis. In 1 horse with chronic renal failure, streptococcal antigens were documented in the diseased glomeruli, although this animal was infected with *S zooepidemicus*.³¹

Agalactia

Agalactia has been reported in broodmares with strangles.¹ Although infection of the mammary glands is possible, the mammary glands are usually normal and the agalactia is thought to be secondary to the fever, anorexia, and lethargy associated with infection. Although generally not life-threatening, this complication may preclude mares from making adequate milk for their foals.

Future Directions

Vaccination

Two recent related research projects will provide DNA genome sequence data for the two closely related bacteria *S equi* and *S zooepidemicus*, which should inform future strategies for strangles vaccine research:

- In 2000 the Home of Rest for Horses funded the *Streptococcus equi* genome-sequencing project at the Wellcome Trust Sanger Institute (http://www.sanger.ac.uk/Projects/S_equi/).
- In 2003 the Horserace Betting Levy Board funded the sequencing of the genome of *S zooepidemicus* (http://www.sanger.ac.uk/Projects/S_zooepidemicus/) at the same Institute.

www.sanger.ac.uk/Projects/S_zooepidemicus/) at the same Institute.

- Comparison of the genome sequences from these bacteria should help identify specific mechanisms by which *S equi* is able to cause abscessation in horses whereas *S zooepidemicus* generally does not.
- This information will be used to identify a protein located on the bacterium's surface and toxins secreted by it that together enable *S equi* to infect and cause disease.
- Key genes have been systematically removed from the *S equi* genome using novel DNA modification techniques in order to attenuate the organism's virulence.
- These modified *S equi* are currently undergoing extensive in vitro laboratory testing as candidates for "live" vaccines.
- In addition, a number of bacterial proteins have been produced and shown to be recognized by the horse's immune system during the course of natural *S equi* infections.
- In time, the best "live" and "subunit" vaccine candidates will be tested initially in mice and, depending on results, subsequently in small numbers of horses in order to demonstrate that they are both safe and effective against challenge infection with *S equi*.
- This will then be followed by clinical vaccine trials to evaluate efficacy in the natural disease setting.

Serological detection of the Carrier State

- A serological test to identify subclinical carriers of *S equi* would be an extremely useful tool in the control of strangles and prevention of new outbreaks.
- The *S equi* and *S zooepidemicus* genome sequencing projects will greatly assist in the identification of proteins useful in immunodiagnosis.

Footnotes

^a EBI, IDEXX, Lexington, KY

References

1. Sweeney CR, Whitlock RH, Meirs DA, et al. Complications associated with *Streptococcus equi* infection on a horse farm. J Am Vet Med Assoc 1987;191:1446-1448.
2. Lindmark H, Jacobson K, Frykberg L, et al. Fibronectin-binding protein of *Streptococcus equi* subsp. *zooepidemicus*. Infect Immun 1996;64:3993-3999.
3. Mukhtar MM, Timoney JF. Chemotactic response of equine polymorphonuclear leucocytes to *Streptococcus equi*. Res Vet Sci 1988; 45:225-229.
4. Spoor-makers TJ, Ensink JM, Goehring LS, et al. Brain abscesses as a metastatic manifestation of strangles: Symptomatology and the use of magnetic resonance imaging as a diagnostic aid. Eq Vet J 2003; 35:146-151.
5. Evers WD. Effect of furaltadone on strangles in horses. J Am Vet Med Assoc 1968;152:1394-1398.
6. Chanter N, Newton JR, Wood JLN, et al. Detection of strangles carriers. Vet Rec 1998;142:496.
7. Newton JR, Wood JLN, Dunn KA, et al. Naturally occurring persistent and asymptomatic infection of the guttural pouches of horses with *Streptococcus equi*. Vet Rec 1997;140:84-90.

8. Galán JE, Timoney JF. Mucosal nasopharyngeal immune response of the horse to protein antigens of *Streptococcus equi*. *Infect Immun* 1985;47:623–628.
9. Todd TG. Strangles. *J Comp Path Therap* 1910;23:212–229.
10. Hamlen HJ, Timoney JF, Bell RJ. Epidemiologic and immunologic characteristics of *Streptococcus equi* infection in foals. *J Am Vet Med Assoc* 1994;204:768–775.
11. Timoney JF, Galán JE. The immune response of the horse to an avirulent strain of *Streptococcus equi*. In: Kimura Y, Kotami S, Shiokawa Y, eds. *Recent Advances in Streptococci, Streptococcal Diseases*. Bracknell, UK: Reedbooks; 1985:294–295.
12. Sheoran AS, Sponseller BT, Holmes MA, et al. Serum and mucosal antibody isotype responses to M-like protein (SeM) of *Streptococcus equi* in convalescent and vaccinated horses. *Vet Immunol Immunopathol* 1997;59:239–251.
13. Galán JE, Timoney JF. Molecular analysis of the M protein of *Streptococcus equi* and cloning and expression of the M protein gene in *Escherichia coli*. *Infect Immun* 1987;55:3181–3187.
14. Jorm LR. Laboratory studies on the survival of *Streptococcus equi* subspecies *equi* on surfaces. In: Plowright W, Rosedale PD, Wade JF, eds. *Proceedings of Equine Infectious Diseases VI*. Newmarket, UK: R & W Publications Ltd; 1992:39–43.
15. Timoney JF, Artiushin SC. Detection of *Streptococcus equi* in equine nasal swabs and washes by DNA amplification. *Vet Rec* 1997;141:446–447.
16. Timoney JF, Trachman J. Immunologically reactive proteins of *Streptococcus equi*. *Infect Immun* 1985;48:29–34.
17. Newton JR, Verheyen K, Talbot NC, et al. Control of strangles outbreaks by isolation of guttural pouch carriers identified using PCR and culture of *Streptococcus equi*. *Equine Vet J* 2000;32:515–526.
18. Timoney JF, Artiushin SC, Boschwitz JS. Comparison of the sequences and functions of *Streptococcus equi* M-like proteins SeM and SzPSe. *Infect Immun* 1997;65:3600–3605.
19. Bazely PL. Studies with equine streptococci: 4. Cross-immunity to *S. equi*. *Aust Vet J* 1942;18:189–194.
20. Bazely PL. Studies with equine streptococci: 3. Vaccination against strangles. *Aust Vet J* 1942;18:141–155.
21. Hoffman AM, Staempfli HR, Prescott JF. Field evaluation of a commercial M protein vaccine against *Streptococcus equi* infection in foals. *Am J Vet Res* 1991;52:589–595.
22. Verheyen K, Newton JR, Talbot NC, et al. Elimination of guttural pouch infection and inflammation in asymptomatic carriers of *Streptococcus equi*. *Equine Vet J* 2000;32:527–532.
23. Piche CA. Clinical observations on an outbreak of strangles. *Can Vet J* 1984;25:7–11.
24. Ensink JM, Smit JA, Van Duijkeren E. Clinical efficacy of trimethoprim/sulfadiazine and procaine penicillin G in a *Streptococcus equi* subsp. *zooepidemicus* infection model in ponies. *J Vet Pharmacol Therap* 2003;26:247–252.
25. Ford J, Lokai MD. Complications of *Streptococcus equi* infection. *Equine Pract* 1980;4:41–44.
26. Judy CE, Chaffin MK, Cohen ND. Empyema of the guttural pouch (auditory tube diverticulum) in horses: 91 cases (1977–1997). *J Am Vet Med Assoc* 1999;215:1666–1670.
27. Pusteria N, Watson JL, Affolter VK, et al. Purpura haemorrhagica in 53 horses. *Vet Rec* 2003;153:118–121.
28. Heath SE, Geor RJ, Tabel H, et al. Unusual patterns of serum antibodies to *Streptococcus equi* in two horses with purpura haemorrhagica. *J Vet Intern Med* 1991;5:263–267.
29. Galán JE, Timoney JF. Immune complexes in purpura haemorrhagica of the horse contain IgA and M antigen of *Streptococcus equi*. *J Immunol* 1985;135:3134–3137.
30. Valberg SJ, Bullock P, Hogetvedt W, et al. Myopathies associated with *Streptococcus equi* infections in horses. *Proc Am Assoc Equine Pract* 1996;42:292–293.
31. Divers TJ, Timoney JF, Lewis RM, et al. Equine glomerulonephritis and renal failure associated with complexes of group-C streptococcal antigen and IgG antibody. *Vet Immunol Immunopathol* 1992;32:93–102.